INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 99/01835

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565 A61K38/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PUROHIT A.: "Inhibition of tumor necrosis factor a-stimulated aromatase activity by microtubule-stabilizing agents, paclitaxel and 2-methoxyestradiol" BIOCHEM BIOPHYS RES COMM, vol. 261, 1999, pages 214-217, XP002121930 abstract page 214, column 2, paragraph 3 page 216, column 2 --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1999	25/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	REED M. J. ET AL: "The role of cytokines and sulphatase inhibitors in regulating oestrogen synthesis in breast tumours" J. STEROID BIOCHEM MOLEC. BIOL., vol. 53, no. 1-6, June 1995 (1995-06), pages 413-420, XP002121931 abstract see conclusions page 419 page 417, column 2, paragraph 1 ---	1-24
Y,P	LI P -K ET AL: "Development of potent non-estrogenic estrone sulfatase inhibitors - Potential affinity labels of human placental aromatase" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 63, no. 7-8, July 1998 (1998-07), page 425-432 XP004134764 ISSN: 0039-128X	1-24
X	see scheme 1,2 abstract; figures 2,3 ---	20-23
Y	PUROHIT A ET AL: "REGULATION OF AROMATASE AND SULPHATASE IN BREAST TUMOUR CELLS" JOURNAL OF ENDOCRINOLOGY,GB,BRISTOL, vol. 150, page S65-S71 XP002054919 ISSN: 0022-0795 abstract page S67 -page S68 ---	1-24
P,Y	GB 2 331 988 A (UNIV BATH ;IMPERIAL COLLEGE (GB)) 9 June 1999 (1999-06-09) page 10 -page 11; examples 1,4,5	1-19
P,X	claims 7,11,12 ---	20-23
Y	PUROHIT A. ET AL: "The development of A-ring modified analogues of oestrone-3-o-sulphamate as potent steroid sulphatase inhibitors with reduced oestrogenicity" J. STEROID BIOCHEM. MOLEC. BIOL, vol. 64, no. 5-6, 1998, pages 269-275, XP000852568	1-19
X	abstract; figures 1,3,4 ---	20-23
Y,P	PUROHIT A. ET AL: "Recent advances in the development of steroid sulphatase inhibitors" J. STEROID. BIOCHEM. MOLEC.BIOL., vol. 69, 1999, pages 227-238, XP000852540	1-19
X	abstract; figure 1 ---	20-23

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INTERNATIONAL SEARCH REPORT

International lication No
PCT/GB 99/01835

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	SIMONS M. H.: "Regulatie en inhibitie van oestronsulfatase-activiteit" PHARMACEUTISCH WEEKBLAD, vol. 131, no. 19, 1996, pages 549-550, XP000852580 abstract	1-23
Y	WO 97 14712 A (JENAPHARM GMBH) 24 April 1997 (1997-04-24)	1-19
X	abstract page 6, line 5-10; claim 1	20-23
Y,P	PUROHIT A. ET AL: "The regulation of oestrone sulphate formation in breast cancer cells" J. STEROID BIOCHEM MOLEC. BIOL., vol. 68, 1999, pages 129-135, XP000852538 abstract page 132, column 2	1-23
P,Y	WO 98 24802 A (POTTER BARRY VICTOR LLOYD ;REED MICHAEL JOHN (GB); IMPERIAL COLLEG) 11 June 1998 (1998-06-11)	1-19
P,X	page 22; figures 1,6-9	20-23
E	WO 99 33858 A (STANFORD RES INST INT) 8 July 1999 (1999-07-08) page 5 page 11 page 16	1-19
X,P	page 64; claims 3,8,13; example 20	20-23
E	EP 0 934 949 A (TEIKOKU HORMONE MFG CO LTD) 11 August 1999 (1999-08-11)	1-19
P,X	abstract; claims 2,4,6	20-23
P,Y	WO 99 03876 A (DUQUESNE UNIVERSITY OF THE HOL) 28 January 1999 (1999-01-28)	1-19
P,X	claims 1,2; figures 2,3; example 3	20-23

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INTERNATIONAL SEARCH REPORT

Interna. al application No.
PCT/GB 99/01835

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first she t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 21 and 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

claims 1-23 partially, 24 complete

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-23 partially, 24 complete

Present claims 1-23 relate to a composition defined by reference to a number of parametric expressions: The expression "a compound comprising a sulphamate group" in claim 1 does neither specify the structural type of such compounds, nor any of its further substituents. It is self-evident that a complete search is not possible for such subject matters. The further definition of such compound as an inhibitor of oestrone sulphatase introduces a functional parameter which is not suitable for identifying compounds in structural terms. Equally the further definition of such compound by the requirement that if the sulphamate group were to be replaced with a sulphate group, then the sulphate compounds would be hydrolysable by a steroid sulphatase enzyme, does not provide a useful definition of a compound in structural terms. Also the further definition of such compound as a cyclic or polycyclic compound is insufficient for structural identification. Even the definition that the sulphamate compound has a "steroidal structure" is obscure to a very high extent in view of the explanation given in the description on pages 11-12. The further definitions of substituents positions and substituents are not particularly helpful in this situation; the expressions "oxyhydrocarbyl", "hydrocarbyl" appear not to have the meanings that are usual in the technical field in question, in view of the explanations on page 8. "C1-6 O" is a group which chemically appears to be meaningless. The preferred compound mentioned in claim 15 is the only sulphamate compound which is fully defined in the claims.
The expression "a biological response modifier" is open for various interpretations and the definition on page 5 of the description is open-ended, as it is evident from the use of "etc". It is clear that in this situation a meaningful search over the whole scope of all claims is not possible.
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.
Moreover present claims relate to an extremely large number of possible compounds/compositions/uses taking into account the definition of these compounds/compositions and uses as given in the description. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been restricted to the embodiments mentioned in the examples and to the compounds/compositions specifically mentioned in the claims and to obvious variants thereof and to the general idea underlying the present application.
Because there is no technical feature defined in claim 24, a search for this claim is not possible (Art 6 PCT; Rule 6.2 (a) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inform.. on on patent family members

International lication No
PCT/GB 99/01835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2331988 A	09-06-1999	AU 1345699 A	16-06-1999
		WO 9927935 A	10-06-1999
WO 9714712 A	24-04-1997	DE 19540233 A	24-04-1997
		AT 178903 T	15-04-1999
		AU 1436097 A	07-05-1997
		BR 9610905 A	13-07-1999
		CN 1200126 A	25-11-1998
		DE 59601683 D	20-05-1999
		EP 0862577 A	09-09-1998
		ES 2131972 T	01-08-1999
		JP 11505268 T	18-05-1999
		US 5705495 A	06-01-1998
WO 9824802 A	11-06-1998	AU 5402398 A	29-06-1998
		EP 0942919 A	22-09-1999
WO 9933858 A	08-07-1999	AU 1941699 A	19-07-1999
EP 0934949 A	11-08-1999	AU 4219197 A	02-04-1998
		WO 9811124 A	19-03-1998
WO 9903876 A	28-01-1999	US 5880115 A	09-03-1999
		AU 8568798 A	10-02-1999

Filed with Demand 6/1/2000

CLAIMS

1. A composition comprising

i) a compound comprising a sulphamate group ("a sulphamate compound"); and

ii) a biological response modifier.

2. A composition according to claim 1 wherein the biological response modifier is a cytokine.

3. A composition according to claim 2 wherein the cytokine is tumour necrosis factor (TNF).

4. A composition according to any one of the preceding claims wherein the sulphamate compound is suitable for use as an inhibitor of oestrone sulphatase (E.C. 3.1.6.2).

5. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound then the sulphate compound would be hydrolysable by a steroid sulphatase enzyme (E.C.3.1.6.2).

6. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37°C it would provide a K_m value of less than 50 mM.

7. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37°C it would provide a K_m value of less than 50 μM.

Filed with Demand 6/1/2000

8. A composition according to any one of the preceding claims wherein the sulphamate compound is a cyclic compound.

9. A composition according to any one of the preceding claims wherein the sulphamate compound is a polycyclic compound.

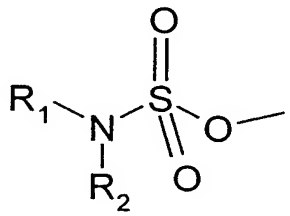
10. A composition according to any one of the preceding claims wherein the sulphamate compound has a steroidal structure.

11. A composition according to claim 10 wherein the sulphamate compound has at least one sulphamate group attached to the 3 position of the A ring of the steroidal nucleus.

12. A composition according to any one of the preceding claims wherein the sulphamate compound comprises at least one oxyhydrocarbyl group, preferably a group of the formula $C_{1-6}O$.

13. A composition according to claim 12 wherein the group $C_{1-6}O$ is attached to the 2 position of the A ring of a steroidal nucleus.

14. A composition according to any one of the preceding claims wherein the sulphamate group of the sulphamate compound has the formula:



wherein each of R_1 and R_2 is independently selected from H or a hydrocarbyl group.

15. A composition according to any one of the preceding claims wherein the sulphamate compound is oxyhydrocarbyl steroidal sulphamate compound (preferably 2-methoxyoestrone-3-*O*-sulphamate), or a pharmaceutically active salt thereof.

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16. A composition according to any one of the preceding claims, wherein the composition further comprises a pharmaceutically acceptable carrier, diluent, or excipient.

17. A composition according to any one of the preceding claims, wherein the compound comprising a sulphamate group is 2-methoxyoestrone-3-*O*-sulphmate, and the biological response modifier is tumor necrosis factor α (TNF-α)

18. A composition according to any one of the preceding claims for use in medicine.

19. Use of a composition according to any one of the preceding claims in the manufacture of a medicament to prevent and/or inhibit tumour growth.

20. Use of a composition according to any one of the preceding claims in the manufacture of a medicament to do any one or more of:

prevent or suppress glucose uptake by a tumour;
prevent and/or inhibit tumour angiogeneis;
disrupt microtubules;
induce apoptosis.

21. Use of an oxyhydrocarbyl steroidal sulphamate compound in the manufacture of a medicament to do any one or more of:

prevent or suppress glucose uptake by a tumour;
prevent and/or inhibit tumour angiogeneis;
disrupt microtubules;
induce apoptosis.

22. A method of treatment comprising administering to a subject in need of treatment a composition according to any one of the preceding claims.

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6/1/2000

23. A method of treatment comprising administering to a subject in need of treatment a composition according to any one of the preceding claims or an oxyhydrocarbyl steroidal sulphamate compound in order to prevent or suppress glucose uptake by a tumour; and/or prevent and/or inhibit tumour angiogeneis; and/or disrupt microtubules; and/or induce apoptosis.

24. A composition that is capable of affecting hormonal activity and is capable of affecting an immune response, wherein the composition is the according to any one of the preceding claims.

25. A composition substantially as described herein.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P004713WO DAA

Box No. I TITLE OF INVENTION

Composition

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

Imperial College of Science, Technology and Medicine
Sherfield Building
Exhibition Road
London
SW7 2AZ
United Kingdom

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☑ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

University of Bath
Claverton Down
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BA2 7AY
United Kingdom

This person is:

☑ applicant only

☐ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(i.e. country)* of nationality: United Kingdom

State *(i.e. country)* of residence: United Kingdom

This person is applicant for the purposes of: ☐ all designated States ☑ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☑ Further applicant and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☑ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

REED, Michael John
42 Wimborne Gardens
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W13 8B3
United Kingdom

This person is:

- ☐ applicant only
- ☑ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☑ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

POTTER, Barry Victor Lloyd
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United Kingdom

This person is:

- ☐ applicant only
- ☑ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☑ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☑ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☑ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☑ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☑ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, please specify on dotted line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☑ AL Albania
- ☑ AM Armenia
- ☑ AT Austria
- ☑ AU Australia
- ☑ AZ Azerbaijan
- ☑ BA Bosnia and Herzegovina
- ☑ BB Barbados
- ☑ BG Bulgaria
- ☑ BR Brazil
- ☑ BY Belarus
- ☑ CA Canada
- ☑ CH AND LI Switzerland and Liechtenstein
- ☑ CN China
- ☑ CU Cuba
- ☑ CZ Czech Republic
- ☑ DE Germany
- ☑ DK Denmark
- ☑ EE Estonia
- ☑ ES Spain
- ☑ FI Finland
- ☑ GB United Kingdom
- ☑ GD Grenada
- ☑ GE Georgia
- ☑ GH Ghana
- ☑ GM Gambia
- ☑ HR Croatia
- ☑ HU Hungary
- ☑ ID Indonesia
- ☑ IL Israel
- ☑ IN India
- ☑ IS Iceland
- ☑ JP Japan
- ☑ KE Kenya
- ☑ KG Kyrgyzstan
- ☑ KP Democratic People's Republic of Korea
- ☑ KR Republic of Korea
- ☑ KZ Kazakhstan
- ☑ LC Saint Lucia
- ☑ LK Sri Lanka
- ☑ LR Liberia
- ☑ LS Lesotho
- ☑ LT Lithuania
- ☑ LU Luxembourg
- ☑ LV Latvia
- ☑ MD Republic of Moldova
- ☑ MG Madagascar
- ☑ MK The former Yugoslav Republic of Macedonia
- ☑ MN Mongolia
- ☑ MW Malawi
- ☑ MX Mexico
- ☑ NO Norway
- ☑ NZ New Zealand
- ☑ PL Poland
- ☑ PT Portugal
- ☑ RO Romania
- ☑ RU Russian Federation
- ☑ SD Sudan
- ☑ SE Sweden
- ☑ SG Singapore
- ☑ SI Slovenia
- ☑ SK Slovakia
- ☑ SL Sierra Leone
- ☑ TJ Tajikistan
- ☑ TM Turkmenistan
- ☑ TR Turkey
- ☑ TT Trinidad and Tobago
- ☑ UA Ukraine
- ☑ UG Uganda
- ☑ US United States of America
- ☑ UZ Uzbekistan
- ☑ VN Viet Nam
- ☑ YU Yugoslavia
- ☑ ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after the issuance of this sheet:

- ☑ AE United Arab Emirates
- ☑ ZA South Africa
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. IV

PURVIS, William Michael Cameron
COTTER, Ivan John
PILCH, Adam John Michael
CRISP, David Norman
ROBINSON, Nigel Alexander Julian
HARRIS, Ian Richard
HARDING, Charles Thomas
TURNER, James Arthur
MALLALIEU, Catherine Louise
PRATT, Richard Wilson
PRICE, Paul Anthony King
HOLMES, Miles
HORNER, David Richard
MASCHIO, Antonio
NACHSHEN, Neil
POTTER, Julian
ALCOCK, David

Box No. VI PRIORITY CLAIM

☐ Further priority claims are indicated in the Supplemental Box

The priority of the following earlier application(s) is hereby claimed:

	Filing Date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application: * regional Office	international application: receiving Office
item (1)	10 Jun 1998 10/6/1998	9812535.4	UK		
item (2)	30 Apr 1999 30/4/1999	9910167.7	UK		
item (3)					

☑ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s) : (1) and (2)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number: Country (or regional Office):

Box No. VII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	5
description (excluding sequence listing part)	:	41
claims	:	4
abstract	:	1
drawings	:	9
sequence listing part of description	:	
Total number of sheets	:	60

This international application is accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority documents(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☑ other *(specify):* Letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

DAVID ALCOCK

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings:
   - ☐ received:
   - ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

DEMAND

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: P004713WO CTH DAA

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB99/01835	10 Jun 1999	10 Jun 1998

Title of invention: Composition

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Sterix Limited
The Magdalen Centre
Robert Robinson Avenue
The Oxford Science Park
Oxford
OX4 4GA
United Kingdom

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

REED, Michael John
42 Wimborne Gardens
London
W13 8B3
United Kingdom

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

POTTER, Barry Victor Lloyd
University of Bath
Department of MedicinalChemistry
Claverton Down
Bath BA2 7AY
United Kingdom

State *(that is, country)* of nationality: United Kingdom

State *(that is, country)* of residence: United Kingdom

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/GB99/01835

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☑ agent ☐ common representative

and ☑ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ALCOCK, David
D Young & Company
21 New Fetter Lane
London
EC4A 1DA
United Kingdom

Telephone No.: 023 8063 4816

Facsimile No.: 023 8022 4262

Teleprinter No.: 477667 YOUNGS G

☐ **Address for Correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments: *

1. The applicant wishes the international preliminary examination **to start on the basis of:**

☐ the international application as originally filed

the description
☑ as originally filed
☐ as amended under Article 34

the claims
☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☑ as amended under Article 34

the drawings
☑ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired).*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination:

☑ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

International application No.
PCT/GB99/01835

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only	
				received	not received
1.	translation of international application	:	sheets	☐	☐
2.	amendments under Article 34	: 4	sheets	☐	☐
3.	copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4.	copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5.	letter	: 1	sheets	☐	☐
6.	other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

DAVID ALCOCK

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

PATENT COOPERATION TREATY

SOUTHAMPTON
18 SEP 2000

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ALCOCK, David
D. YOUNG & CO.
21 New Fetter Lane
London EC4A 1DA
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.09.2000
Applicant's or agent's file reference P004713WO CTH DAA	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01835	10/06/1999	10/06/1998

Applicant
STERIX LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P004713WO CTH DAA		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01835	10/06/1999	10/06/1998
International Patent Classification (IPC) or national classification and IPC A61K31/565		
Applicant STERIX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/01/2000	14.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Toulacis, C Telephone No. +49 89 2399 8638

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01835

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-41	as originally filed

Claims, No.:

1-25	as received on	20/03/2000	with letter of	15/03/2000

Drawings, sheets:

1/9-9/9	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 5-16, 18-25.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5-16, 18-25 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. (1-16, 18-24) all partially, 25 complete.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 17
	No:	Claims
Inventive step (IS)	Yes:	Claims 17
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 17
	No:	Claims

2. Citations and explanations

see separate sheet

III

The search has been carried out for those parts of the application which are clear (and/or concise), namely the compounds as defined in claim 17 and for those parts of claims 1-16 and 18-24 referring to said clearly defined compounds.
Claim 25 has completely not been searched (see search report; sheet PCT/ISA/210).
Consequently, the examination can only be carried out for those parts of the application which have been searched, namely claim 17 and claims 1-16 and 18-24 when referring to the compounds as defined in claim 17.

Additionally, the expression "wherein **if** the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound then the sulphate compound would be hydrolysable by a steroid sulphatase enzyme (E.C.3.1.6.2)") in claims 5-16, 18-24 is unclear and renders said claims unclear regarding the scope of protection (Art. 6 PCT).
The subject-matter of claim 25 is additionally not clear due to the expression "as substantially described herein".
Furthermore, the subject-matter of claims 20, 21 and 23 is not supported by the description (Art. 6 PCT).
Claims 20, 21 and 23 are directed to the use of a composition according to the presently claimed invention, in the manufacture of a medicament to do any one or more of: i) prevent or suppress glucose uptake by a tumour, ii) prevent and/or inhibit tumour angiogenesis, iii) disrupt microtubules and iv) induce apoptosis.
The effects of i) to iii) are not supported by the description for the composition claimed comprising the combination of a) a compound comprising a sulfamate group and b) a biological response modifier. Only the effect of iv) is supported by the description for the composition claimed, whereas the effects of i) and iv) are supported for the compound 2-methoxy EMATE and not the combination.
The effects, however, of 2-methoxy EMATE are already known (see D1, page 414, right column, last paragraph).

V

Claims 1-16, 18-24 (when the compound comprising a sulphamate group is 2-methoxyoestrone-3-O-sulphamate and the biological response modifier is tumour necrosis factor alpha)

(N) A composition comprising i) 2-methoxyoestrone-3-O-sulphamate and ii) tumour necrosis factor alpha, is not disclosed in the documents cited in the search report.

(IS) The object of the present application is to provide a composition suitable for use in the treatment of cancers and especially breast cancer (description; page 3, lines 22-23). Said object has been achieved by providing a composition comprising i) 2-methoxyoestrone-3-O-sulphamate and ii) tumour necrosis factor alpha (see description, page 34, table III and page 35, lines 5-8 in context with figures 9 and 10). It is shown that the combination of 2-methoxy EMATE and TNFa enhance apoptosis of MCF-7 breast cancer cells (fig. 9), and decrease the tumour volume of an NMU-induced mammary tumour significantly, compared to the components alone.
Document, REED M. J. ET AL: "The role of cytokines and sulphatase inhibitors in regulating oestrogen synthesis in breast tumours" J. STEROID BIOCHEM MOLEC. BIOL., vol. 53, no. 1-6, June 1995 (1995-06), pages 413-420, XP002121931 **(D1)**, discloses that a number of growth factors and cytokines (corresponding to the claimed TNFa), stimulate the activities of enzymes involved in oestrogen synthesis in breast cancer cells, whereas EMATE (corresponding to the claimed 2-methoxy EMATE) inhibits oestrone sulphatase (E1-STS), (D1; abstract; page 415, right column, paragraph 2; fig. 4, 6; conclusions).
Said results of D1 concerning the cytokines is prejudicial for the combination of an oestrone sulphatase inhibitor (2-methoxy EMATE) with a cytokine as TNFa.

(IA) The industrial applicability of the compositions is beyond any doubt.

CLAIMS

1. A composition comprising

i) a compound comprising a sulphamate group ("a sulphamate compound"); and

ii) a biological response modifier.

2. A composition according to claim 1 wherein the biological response modifier is a cytokine.

3. A composition according to claim 2 wherein the cytokine is tumour necrosis factor (TNF).

4. A composition according to any one of the preceding claims wherein the sulphamate compound is suitable for use as an inhibitor of oestrone sulphatase (E.C. 3.1.6.2).

5. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound then the sulphate compound would be hydrolysable by a steroid sulphatase enzyme (E.C.3.1.6.2).

6. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37°C it would provide a K_m value of less than 50 mM.

7. A composition according to any one of the preceding claims wherein if the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37°C it would provide a K_m value of less than 50 μM.

8. A composition according to any one of the preceding claims wherein the sulphamate compound is a cyclic compound.

9. A composition according to any one of the preceding claims wherein the sulphamate compound is a polycyclic compound.

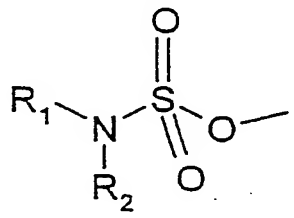
10. A composition according to any one of the preceding claims wherein the sulphamate compound has a steroidal structure.

11. A composition according to claim 10 wherein the sulphamate compound has at least one sulphamate group attached to the 3 position of the A ring of the steroidal nucleus.

12. A composition according to any one of the preceding claims wherein the sulphamate compound comprises at least one oxyhydrocarbyl group, preferably a group of the formula $C_{1-6}O$.

13. A composition according to claim 12 wherein the group $C_{1-6}O$ is attached to the 2 position of the A ring of a steroidal nucleus.

14. A composition according to any one of the preceding claims wherein the sulphamate group of the sulphamate compound has the formula:



wherein each of R_1 and R_2 is independently selected from H or a hydrocarbyl group.

15. A composition according to any one of the preceding claims wherein the sulphamate compound is oxyhydrocarbyl steroidal sulphamate compound (preferably 2-methoxyoestrone-3-*O*-sulphamate), or a pharmaceutically active salt thereof.

16. A composition according to any one of the preceding claims, wherein the composition further comprises a pharmaceutically acceptable carrier, diluent, or excipient.

17. A composition according to any one of the preceding claims, wherein the compound comprising a sulphamate group is 2-methoxyoestrone-3-*O*-sulphmate, and the biological response modifier is tumor necrosis factor α (TNF-α)

18. A composition according to any one of the preceding claims for use in medicine.

19. Use of a composition according to any one of the preceding claims in the manufacture of a medicament to prevent and/or inhibit tumour growth.

20. Use of a composition according to any one of the preceding claims in the manufacture of a medicament to do any one or more of:

prevent or suppress glucose uptake by a tumour;
prevent and/or inhibit tumour angiogeneis;
disrupt microtubules;
induce apoptosis.

21. Use of an oxyhydrocarbyl steroidal sulphamate compound in the manufacture of a medicament to do any one or more of:

prevent or suppress glucose uptake by a tumour;
prevent and/or inhibit tumour angiogeneis;
disrupt microtubules;
induce apoptosis.

22. A method of treatment comprising administering to a subject in need of treatment a composition according to any one of the preceding claims.

M 20-03-00

23. A method of treatment comprising administering to a subject in need of treatment a composition according to any one of the preceding claims or an oxyhydrocarbyl steroidal sulphamate compound in order to prevent or suppress glucose uptake by a tumour; and/or prevent and/or inhibit tumour angiogeneis; and/or disrupt microtubules; and/or induce apoptosis.

24. A composition that is capable of affecting hormonal activity and is capable of affecting an immune response, wherein the composition is the according to any one of the preceding claims.

25. A composition substantially as described herein.

PATENT COOPERATION TREATY

SOUTHAMPTON
FEB 2000
PCT

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
ALCOCK, David
D. YOUNG & CO.
21 New Fetter Lane
London EC4A 1DA
GRANDE BRETAGNE

25500

WRITTEN OPINION

(PCT Rule 66)

Records noted

Date of mailing *(day/month/year)*	28.02.2000
Applicant's or agent's file reference: P004713WO CTH DAA	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01835	10/06/1999	10/06/1998

International Patent Classification (IPC) or both national classification and IPC
A61K31/565

Applicant
STERIX LIMITED et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10/10/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Toulacis, C

Formalities officer (incl. extension of time limits)
Hebert, W
Telephone No. +49 89 2399 2152

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-41 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-24,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5-24 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4 (Yes)
Inventive step (IS)	Claims	1-4 (Yes)
Industrial applicability (IA)	Claims	1-4 (Yes)

2. Citations and explanations

see separate sheet

III

Claims 5-24

The expression *"wherein **if** the sulphamate group on the sulphamate compound were to be replaced with a sulphate group to form a sulphate compound then the sulphate compound would be hydrolysable by a steroid sulphatase enzyme (E.C.3.1.6.2)"* in claims 5 to 24 is unclear and renders said claims unclear regarding the scope of protection (Art. 6 PCT).
The subject-matter of claim 24 is additionally not clear due to the expression *"as substantially described herein".*
The subject-matter of claims 19, 20 and 22 is not supported by the description (Art. 6 PCT).
Claims 19, 20 and 22 are directed to the use of a composition according to the presently claimed invention, in the manufacture of a medicament to do any one or more of: *i) prevent or suppress glucose uptake by a tumour, ii) prevent and/or inhibit tumour angiogenesis, iii) disrupt microtubules* and iv) induce apoptosis.
The effects of i) to iii) are not supported by the description for the composition claimed comprising the combination of a) a compound comprising a sulfamate group and b) a biological response modifier. Only the effect of iv) is supported by the description for the composition claimed, whereas the effects of i) and iv) are supported for the compound 2-methoxy EMATE and not the combination.
The effects, however, of 2-methoxy EMATE are already known (see D1, page 414, right column, last paragraph).

V

Claims 1-4

(N) A composition comprising i) a compound comprising a sulfamate group and ii) a biological response modifier, is not disclosed in the documents cited in the search report.

(IS) The object of the present application is to provide a composition suitable for use in the treatment of cancers and especially breast cancer (description; page 3, lines 22-23). Said object has been achieved by providing a composition as defined in

claim 1 of the present application (see description, page 34, table III and page 35, lines 5-8 in context with figures 9 and 10). It is shown that the combination of 2-methoxy EMATE (sulfamate comprising compound) and TFNa (biological response modifier) enhance apoptosis of MCF-7 breast cancer cells (fig. 9), and decrease the tumour volume of an NMU-induced mammary tumour significantly, compared to the components alone.

Document, REED M. J. ET AL: "The role of cytokines and sulphatase inhibitors in regulating oestrogen synthesis in breast tumours" J. STEROID BIOCHEM MOLEC. BIOL., vol. 53, no. 1-6, June 1995 (1995-06), pages 413-420, XP002121931 **(D1)**, discloses that a number of growth factors and cytokines (biological response modifiers), stimulate the activities of enzymes involved in oestrogen synthesis in breast cancer cells, whereas EMATE (sulfamate comprising compound) inhibits oestrone sulphatase (E1-STS), (D1; abstract; page 415, right column, paragraph 2; fig. 4, 6; conclusions).

Said results of D1 concerning the biological response modifiers is prejudicial for the combination of an oestrone sulphatase inhibitor (EMATE) with a biological response modifier as presently claimed.

(IA) The industrial applicability is beyond any doubt.

SOUTHAMPTON
NOV 1999

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

ALCOCK, David
D. Young & Co.
21 New Fetter Lane
London EC4A 1DA
ROYAUME-UNI

Recorded DAA

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 19 November 1999 (19.11.99)	
Applicant's or agent's file reference P004713WO DAA	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/01835	**International filing date** (day/month/year) 10 June 1999 (10.06.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDECINE UNIVERSITY OF BATH	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
STERIX LIMITED The Magdalen Centre Robert Robinson Avenue The Oxford Science Park Oxford OX4 4GA United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
A power of attorney signed by the new applicant is required.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Ting Zhao
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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